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Effect of disease severity and dopaminergic medication on recollection and familiarity in patients with idiopathic nondementing Parkinson's

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ABSTRACT

The effect of disease severity and dopaminergic medication on the assessment of familiarity and the recollection of episodic details during recognition in nondementing idiopathic Parkinson's is uncertain. Some studies have reported familiarity as deficient in mild Parkinson's yet others have found it intact even in moderate Parkinson's. Recollection has been found to be both preserved and deficient in mild and moderate Parkinson's. The extent to which these conflicting findings are explained by disease severity or dopaminergic medication or a combination of the two is uncertain, as all studies assessed patients in a medicated state, and disease severity has not always been consistently reported.

Twelve patients with mild Parkinson's and 11 with moderate Parkinson's (medicated Hoehn and Yahr mean: 2.1 and 3.2, respectively), completed matched versions of a yes/no recognition memory test in a medicated and unmedicated condition (termed ON and OFF, respectively). Twenty-one matched healthy volunteers also completed both memory tasks in 2 separate sessions (termed Blue and Green, respectively).

In the ON/Green condition, the moderate Parkinson's recollection performance was significantly poorer than the healthy volunteers and mild Parkinson's. By contrast, recognition memory and familiarity measures in both Parkinson's group were relatively spared. In the OFF/Blue condition, the moderate Parkinson's recollection was impaired, but only in relation to the healthy volunteer set. There were no significant differences in recollection performance between the mild and moderate Parkinson's groups. Again, recognition memory and familiarity measures in both Parkinson's group were relatively spared. Further analyses showed the moderate patients' recollection rates to be significantly poorer ON-medication compared to OFF.

These findings are discussed in relation to the staging of disease progression on medial temporal areas which separately support recollection and familiarity, and the putative effects the different classes of dopaminergic drugs may have on these areas.

1. Introduction

This study investigated the effect of dopaminergic medication and disease severity on the assessment of familiarity and the recollection of episodic details during recognition in patients with nondementing idiopathic Parkinson's. These processes differ with respect to the type of information that they provide and the level of recognition confidence each typically produces. A widely held view holds that recollection is a high confidence threshold process that involves remembering specific details from episodic memory regarding a past event. By contrast, recognition based on feelings of familiarity varies continuously as a reflection of memory strength in the absence of retrieval of contextual detail (Yonelinas & Jacoby, 1995).

There is conflicting evidence regarding the status of recollection and familiarity at different stages of Parkinson's, with only one study to date examining recollection in patients at different stages of disease severity (Hay, Moscovitch, & Levine, 2002). In this study, recollection was normal in the mild Parkinson's group (Hoehn & Yahr, 1967 rating severity ratings in the range of 1–2.5) but significantly declined in the moderate group (Hoehn and Yahr [HY] 3–4). Familiarity was not assessed. Three other studies have investigated the dual process view of recognition memory, sampling patients at a single disease stage. It is important to note that there was consistency between these studies in relation to

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their use of the remember–know paradigm and adoption of the formulae provided by Yonelinas and Jacoby (1995) to derive estimates of recollection and familiarity. Consistent with Hay et al.'s findings, recollection was spared in mild Parkinson's (mean illness duration = 5.79 years [HY not provided], Davidson, Anaki, Saint-Cyr, Chow, & Moscovitch, 2006) and deficient in moderate Parkinson's (HY 2–3, Edelstyn, Mayes, Condon, Tunnicliffe, & Ellis, 2007), although Barnes, Boubert, Harris, Lee, and David (2003) reported sparing of recollection in moderate Parkinson's (mean HY 2.86) unless the patients had a history of visual hallucinations (mean HY 3.39).

The effect of disease severity on familiarity is also uncertain. In the study by Davidson et al. (2006), familiarity was impaired in mild Parkinson's, whereas both Barnes et al. (2003) and Edelstyn et al. (2007) found it to be preserved in moderate Parkinson's. We have identified four reasons (there may be others) why evidence is not fully concordant. First, although each of these studies assessed medicated patients, not all may have been in an optimally medicated state (e.g., Hay et al., 2002). Second, there is considerable variation between studies in the mode of classifying disease stage. Third, neuropsychological characteristics of patients varied, with executive dysfunction present in some patients (Barnes et al., 2003; Edelstyn et al., 2007; Hay et al., 2002) but not others (Davidson et al., 2006). Fourth, a major problem of studies in this area is the accurate measurement of recollection and familiarity, and particularly of familiarity. This problem applies most strongly to the remember/know procedure where it is well established that procedural differences, inadequate training of participants and inadequate attempts to ensure participants understand the procedure, as may be the case when the remember–know procedure is used in a surprise memory test (e.g., Barnes et al., 2003).

An influential view in Parkinson's research, is that deficits in free recall (Daum et al., 1995; Gabrieli, Singh, Stebbins, & Goetz, 1996; Ivory, Knight, Longmore, & Cardoc-Davies, 1999; Johnson, Pollard, Vernon, Tomes, & Jog, 2005) and recollection (Hay et al., 2002; Barnes et al., 2003) are contingent on a breakdown in prefrontally mediated memory processes underlying long-term memory encoding and retrieval strategies (such as the use of semantic organisation). Strategic memory processes are likely to depend, at least in part, on executive functions such as planning, decision-making and working memory (Shimamura, Janowsky, & Squire, 1991), which therefore places the origin of the recollection deficits within the mesostriatal-frontal system. However, there is a growing body of evidence suggesting disruption of dopamine modulation of mesolimbic structures, includes the ventral tegmental area and the hippocampus, may also contribute to recall and recollection impairments in Parkinson's. Evidence in support of this proposal is reviewed below.

Firstly, animal studies demonstrate a critical role for dopamine in inducing hippocampal long-term potentiation, a form of synaptic plasticity thought to underlie memory storage (Lemon & Manahan-Vaughan, 2006; Mockett, Brooks, Tate, & Abraham; Otmakhova & Lisman, 1996; Wood et al., 2006), mediated by D_1, D_3, D_4 and D_5 dopamine receptors in the CA1–3 fields of the hippocampus (Bentivoglio & Morelli, 2005, chap. 1; Li, Cullen, Anwyl, & Rowan, 2003; Mockett, Guévremont, Williams, & Abraham, 2007; O'Carroll, Martin, Sandin, Frenguelli, & Morris, 2006). Dopamine has also been shown to modulate synaptic plasticity in the perirhinal cortex (Bentivoglio & Morelli, 2005, chap. 1; Cummings et al., 2006; MacDonald, Cervenka, Farde, Nyberg, & Bäckman, 2009), mediated by D_2 receptor (Bentivoglio & Morelli, 2005, chap. 1). It should be noted at this point, that involvement of the hippocampus in recollection and the perirhinal cortex in familiarity has already been proposed in Aggleton and Brown's (1999, 2006) still controversial dual process model of episodic memory.

Secondly, anatomical evidence supporting a role of the mesolimbic circuit in memory comes from a series of functional magnetic imaging studies of healthy older adults. These investigations report a positive correlation between memory formation and integrity/activation of the ventral tegmental area (Bunzeck et al., 2007; Düzel et al., 2008; Kumaran & Düzel, 2008; Wittman, Schiltz, Boehler, & Düzel, 2008). Whilst it appears that reward-related activation of the medial substantia nigra pars compacta is associated with improved hippocampus-dependent memory consolidation (Wittman et al., 2005), encoding-related midbrain activation also occurs independently of reward (Schott et al., 2004). Other evidence that genetic polymorphisms in the dopamine clearance pathways, such as the dopamine transporter (DAT1), affect encoding-related activation patterns in the midbrain and hippocampus (Schott et al., 2006) further supports the case that dopamine plays an important role in memory.

Thirdly, Braak et al. (2003) (see also Braak & Del Tredici, 2008; Braak, Rüb, & Del Tredici, 2006) examined the brains of 41 patients obtained at autopsy ~~by~~ clinical severity and cognitive function unknown at time of death. They proposed that α-synuclein pathology, the most abundant protein in Lewy bodies, spreads in a predictable caudo-rostral direction through the brain, beginning in the medulla oblongata and midbrain, before extending to the CA2 fields of the hippocampus and the transentorhinal region (i.e. the medial portion of the perirhinal cortex, BA 35/35a, Garey, 1999; Van Hoesen & Pandya, 1975; Taylor & Probst, 2008) and on to the association ~~and primary sensory~~ areas and prefrontal cortex (see Kalaitzakis, Graeber, Gentleman, & Pearce, 2008 for a critical discussion of this controversial model). ~~According to~~ Braak et al.'s staging model, memory impairments are predicted based on ~~disruption of~~ medial temporal lobe pathology, and furthermore, hippocampal-dependent memory processes will decline prior to perirhinal-dependent processes, due to relative sparing of lateral perirhinal areas. However, the staging of these memory changes in relation to clinical severity is unclear.

Magnetic resonance (MR) imaging studies of Parkinson's patients using manual volumetric and voxel-based morphometry suggests recall impairments emerge, ~~as early~~ the mild–moderate stages (mean HY 2.5, Ibarretxe-Bilbao et al., 2008) once hippocampal pathology has reached a critical level (Brück, Kurki, Kaasinen, Vahlberg, & Rinne, 2004; Camicoli et al., 2003; Camicioli, Moore, Kerr, & Kaye, 1999; Duda et al., 2009; Laakso et al., 1996; but see Burton, McKeith, Burn, Williams, & O'Brien, 2004; Bouchard et al., 2008; Beyer et al., 2009; Dashtipour et al., 2009; Jokinen et al., 2009).

In sum, the findings from animal research and MR studies of healthy volunteers support a role for dopamine modulation of hippocampal and perirhinal memory processes, and furthermore, post-mortem studies of the brains of Parkinson's patients and MR studies of the hippocampus in nondementing Parkinson's patients indicate both structures are subject to the development of staged pathology.

Dopaminergic medication, and here we are primarily considering l-dopa, can also have a significant effect on cognitive function. Evidence indicates that the requisite dopaminergic state necessary to control motor symptoms has the potential to move the same patient away from their optimum for certain cognitive functions (see "l-dopa overdose hypothesis", described by Gotham, Brown, & Marsden, 1988; Cools, 2006; Cools, Barker, Sahakian, & Robbins, 2001; Rowe et al., 2008), and may even lead to a dopamine dysregulation syndrome, marked by an increase in risk-taking behaviour such as pathological gambling and hypersexuality (Driver-Dunckley, Samanta, & Stacy, 2003; Dodd et al., 2005). The relationship between the efficiency of neuronal activity and the state of dopaminergic modulation in l-dopa overdose hypothesis is represented by a Yerkes-Dodson inverted U-shaped curve with

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cognitive functions declining with deviation away from optimum dopamine levels, indicated by the centre of the curve. Extrapolating this model to recollection and familiarity, implies that l-dopa has the capacity to both improve and impair these kinds of memory depending on baseline dopamine levels in the underlying neural circuitry.

The aim of our ~~investigation~~ was to investigate the impact of disease severity and dopaminergic medication on familiarity and recollection in nondementing idiopathic Parkinson's. The predictions for our study have been informed by the application of the l-dopa overdose hypothesis (Cools, 2006) on dopamine-dependent medial temporal lobe memory circuits, the staging model of α-synuclein pathology in Parkinson's (Braak et al., 2003) and the neural correlates of the dual process view of recognition memory (Aggleton & Brown, 1999, 2006; Yonelinas et al., 2002). Our central hypothesis was that the neural pathways on which recollection and familiarity separately depend, are differentially affected by disease progression, and consequently, the effects of dopaminergic medication on these memory measures will also differ.

The method used in this study to assess the effects of l-dopa on recognition memory, familiarity and recollection is the controlled l-dopa withdrawal procedure. This requires patients to abstain from their dopaminergic medication for a ("wash out") period of 12–18 h prior to the memory assessment. Performance in this OFF state is compared with performance on a separate testing session, taking place at the same time of day as the OFF state, during which patients take their routine medication as usual. This procedure minimises, but does not eliminate, any effects that dopaminergic medication may have on recollection and familiarity. It is also less prone to the confounds of differences in disease severity compared to the alternative of comparing de novo, i.e. never medicated, patients with the same individuals at a later stage after l-dopa administration, or a different already-treated group.

Our first set of predictions applied to patients tested in an unmedicated state. In mild Parkinson's, we expected both recollection and familiarity to be preserved, contingent on the relative preservation of both the hippocampus, lateral and medial perirhinal cortical areas. By contrast, in moderate Parkinson's, a significant decline in recollection was predicted, contingent on developing pathology in the hippocampus. By contrast, relative sparing of familiarity performance was expected, due to preservation of lateral (if not medial) areas of the perirhinal cortex.

The second set of predictions pertained to the performance of the same patients assessed in a fully medicated state. We expected a l-dopa induced impairment of both recollection and familiarity in mild Parkinson's, as routine medication overdosed (close to) optimal dopamine levels in the hippocampus and perirhinal cortex. By contrast, in moderate Parkinson's, l-dopa should have a beneficial effect on recollection, as medication remediated depleted dopamine levels in the hippocampus. Familiarity performance was again expected to show relative sparing, as the same l-dopa which 'overdosed' optimal dopamine levels in the lateral perirhinal cortex also restored depleted levels in medial perirhinal cortex.

2. Participants

Twenty-three Parkinson's patients were recruited from the Parkinson's disease outpatient clinic in the Department of Neurology, University Hospital of North Staffordshire. During a clinical interview (SJE), patients were screened for adverse clinical events or issues (e.g., drastic medication changes, fatigue, distress) that might affect performance.

Medicated patients were subdivided into 2 subgroups based on HY score. Twelve patients rated as stage 1, 2 or 2.5 and classified as mild (mean HY = 2.1, SD = 0.42; mean illness duration = 4.5 years, SD = 2.71), with a further 11 ~~were~~ rated as stage 3 or 4 and classified as moderate (mean HY = 3.2, SD = 0.41; mean illness duration = 8.55 years, SD = 2.84).

Details of the patients' medication regimens are provided in Table 1. There were no significant differences in medication dose between the mild and moderate Parkinson's groups for the second generation nonergoline dopamine agonists ($t(22) = -1.52$, $p = 0.15$), MAO-B inhibitors ($t(22) = -1.45$, $p = 0.16$) or COMT inhibitors ($t(22) = -0.06$, $p = 0.95$). However, l-dopa dose was significantly different ($t(22) = -2.08$, $p = 0.05$), with higher levels in the moderate compared to the mild Parkinson's group.

A single group of 21 healthy volunteers was recruited and served as controls for both the mild and moderate Parkinson's subgroups. The healthy volunteer set matched the mild Parkinson's subgroup for age ($t(31) = 0.7$, $p = 0.49$), premorbid IQ ($t(31) = 1.11$, $p = 0.28$: *National Adult Reading Test* [NART], Nelson & Willison, 1991), current levels of functioning ($t(31) = -1.5$, $p = 0.13$: *Mini-Mental State Examination* [MMSE], Folstein, Folstein, & McHugh, 1975; $t(31) = -0.56$, $p = 0.58$: *The Cambridge Examination for Mental Disorders of the Elderly* [CAMCOG], Roth, Huppert, Mountjoy, & Tym, 1998) and depression scores ($t(31) = -1.7$, $p = 0.11$: *Hamilton Depression Inventory* [HDI], Reynolds & Kobak, 1995).

The ~~same~~ healthy volunteer group also matched the moderate Parkinson's subgroup for age ($t(30) = 0.32$, $p = 0.75$), *NART*: ($t(31) = 1.14$, $p = 1.0$); MMSE: ($t(30) = -1.13$, $p = 0.27$); *CAMCOG*: ($t(30) = 1.49$, $p = 0.15$) but not *HDI*: ($t(30) = -3.11$, $p = 0.004$).

Comparison of motor symptoms ON- and OFF-medication revealed a significant improvement with medication for the mild ($t(31) = -2.5$, $p = 0.03$: *Unified Parkinson's Disease Rating Scale* [*UPDRS*], Fahn & Elton, 1987) and moderate Parkinson's group (*UPDRS*: $t(30) = -3.35$, $p = 0.007$).

The demographic, clinical (patients only) and neuropsychological characteristics of the participant groups are provided in Table 1.

Exclusion criteria for all participants included a MMSE score of 25 or less, presence of neurological or psychiatric history (apart from Parkinson's in the index group), history of substance abuse (such as alcoholism), currently taking antidepressants, learning difficulty (including dyslexia), or English as a second language. Additional exclusion criteria for the patients were visual hallucinations and/or delusions, dyskinesias or commenced dopaminergic medication within the 2 months prior to the study.

3. Procedure

Two versions of a "yes/no" recognition memory test (RMT) were constructed from a pool of 320 4–6 letter words (mean word frequency = 229.2 per million, range 83–1789; mean concreteness = 462.7 and mean imageability = 491.2) using the norms provided by Coltheart (1981) and Baayen, Piepenbrock, and van Rijn (1993). The pool comprised 160 high frequency words (word frequency 229.2 per million, range 83–1789, concreteness = 462.7, imageability = 491.2) and 160 low frequency words (mean word frequency = 1.9 per million, range 1–3, mean concreteness = 472.1, mean imageability = 482.7). Both versions (termed RMT version 1 and RMT version 2) of the recognition memory tests were matched for word frequency (RMT version 1: mean = 115.4 per million, range 1–1461, SD = 160.51; RMT version 2: mean = 115.65 per million, range 1–1789, SD = 160.87), concreteness (RMT version 1: mean = 467.9, SD = 6.36; RMT version 2: mean = 466.9, SD = 8.79) and imageability (RMT version 1: mean = 487.2, SD = 6.08; RMT version 2: mean = 486.5, SD = 5.66), and for the size of relative recollection and familiarity contribution recorded at test.

At study, participants saw a mixture of 80 high frequency and low frequency words for 3-s each (3-s inter-stimulus interval) and

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made a judgement as to whether the word was pleasant, unpleasant or neutral. Immediately after completing the study phase, recognition using the yes/no procedure was tested by presenting each of the studied words (targets) randomly intermixed with 80 high frequency and low frequency new words or lures, that were matched to the targets for mean word frequency, concreteness and imageability. Each word was presented individually, and recognition judgements were made within a 3-s response window.

Correct identification of a target item was defined as a *hit*, whilst false recognition of a lure was termed a *false alarm*. Following each endorsement, irrespective of whether it was a hit or false alarm, participants made a subjective judgement of their recogni-

Table 1
Demographic, neuropsychological and clinical (patients only) characteristics by group.

Group	Gender	Age	MMSE	NART	HDI	CAM	HY	Diag (years)	UPDRS		Medication—daily dose (mg)			
									ON	OFF	L-dopa	Agonists	MAO-B	COMT
Parkinson's disease patients (n = 23)														
PD 6	F	65	28	113	14.3	103	2	5	6	8	300	16	0	0
PD 7	M	75	30	124	1	104	2.5	3	5	13	250	9	0	0
PD 9	M	62	29	126	3.8	103	2.5	4	4	7	250	11	0	0
PD 10	M	59	30	126	4	100	2.5	2	11	11	100	11	0	0
PD 11	F	65	30	125	7.5	98	1	3	8	9	300	0	1	0
PD 12	M	71	30	127	4	98	2	6	10	10	200	7	1	0
PD 16	F	56	30	113	3.2	102	2	2	4	5	100	35	0	0
PD 18	M	64	30	124	11	100	2	4	8	10	100	56	10	0
PD 19	F	68	30	114	6	100	2	3	6	9	100	12	0	0
PD 20	M	63	29	109	8.5	99	2	4	6	6	250	0	0	0
PD 22	M	73	30	124	6.5	102	2.5	6	11	11	400	0	10	0
PD 24	M	71	30	115	3	101	2	12	7	7	300	16	0	0
PD 1	M	75	30	106	7.5	92	3	9	6	11	1000	4	0	0
PD 2	M	58	30	124	10.3	103	3	8	16	20	1200	12	10	0
PD 3	M	77	29	117	9.8	98	3	7	16	15	500	16	0	0
PD 4	M	64	30	98	18.2	101	4	10	20	23	375	24	0	200
PD 5	M	72	28	87	5.2	86	3	10	12	21	800	12	0	0
PD 8	M	64	29	109	3	99	3	6	15	17	250	16	1	0
PD 13	M	53	30	117	8.8	97	3	5	13	15	450	3	0	0
PD 14	M	69	30	123	10.7	100	3	14	14	17	525	16	5	0
PD 15	F	79	29	107	8.4	98	3	8	16	17	412.5	0	0	200
PD 17	F	76	30	123	7	100	4	12	17	17	1000	0	10	0
PD 23	M	55	30	118	4	100	3	5	7	7	450	12	0	0
Mean	17M/7F	66.7	29.57	115.7	7.2	99.3	2.61	6.43	10.3	12.43	417.93	12.52	2.09	17.39
SD		7.48	0.73	10.18	4.04	3.87	0.69	2.84	4.75	5.16	306.3	12.76	3.86	57.62
Mild PD subgroup (n = 12)														
Mean	8M/4F	66	29.67	120	6.07	100.8	2.08	4.5	7.17	8.83	220.83	14.42	1.83	0
SD		5.75	0.65	6.56	3.78	1.99	0.42	2.71	2.48	2.33	101.04	16.22	3.83	0
Moderate PD subgroup (n = 11)														
Mean	9M/2F	67.5	29.5	111.7	8.45	97.64	3.18	8.55	13.8	16.36	632.95	10.46	2.36	36.36
SD		9.25	0.81	11.67	4.11	4.76	0.41	2.84	4.19	4.48	312.56	7.741	4.06	80.9
Healthy volunteers (n = 21)														
HV 1	F	59	29	119	3	102								
HV 2	F	64	28	113	3.5	100								
HV 3	F	60	30	121	2.7	102								
HV 4	M	66	30	119	2.2	102								
HV 5	M	64	29	109	3	101								
HV 6	M	72	30	121	0.7	99								
HV 7	M	79	29	118	4	103								
HV 8	F	64	30	124	11.4	102								
HV 9	M	79	30	120	3.4	100								
HV 10	F	50	28	116	1	99								
HV 11	M	73	29	122	6.4	103								
HV 12	F	77	26	110	5	90								
HV 13	M	79	28	106	5.9	92								
HV 14	M	67	30	118	4.2	102								
HV 15	F	71	30	119	7	103								
HV 16	M	77	30	124	3	104								
HV 17	M	60	30	122	2	104								
HV 18	M	72	29	101	9	101								
HV 19	M	68	30	110	1	98								
HV 20	M	54	29	107	4.4	99								
HV 21	M	69	28	102	7	100								
Mean	14M/7F	67.8	29.14	115.3	4.28	100.3								
SD		8.29	1.062	7.149	2.79	3.538								

Notes: Mild Parkinson's (PD) subgroup consists of the following patients: PD 6, 7, 9–12, 16, 18–20, 22, 24; moderate PD subgroup: PD 1–5, 8, 13–15, 17, 23. SD, 1standard deviation; MMSE, Mini-Mental State examination; NART, National Adult Reading Test; HDI, Hamilton Depression Inventory; CAM, The Cambridge Examination for Mental Disorders of the Elderly—Revised; HY, Hoehn and Yahr; Diag, years since diagnosis; UPDRS, Unified Parkinson's Disease Rating Scale; ON, medicated state; OFF, unmedicated state; agonists: ropinirole, pramipexole and rotigotine; COMT, catechol-*O*-methyl transferase inhibitors: tolcapone and entacapone; MAO-B, monoamine oxidase-B inhibitors: selegiline and rasagiline.

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Table 2
Mean hit and false alarm rates for recognition memory, know and remember rates in ON/Green and OFF/Blue conditions by group.

Group	Recognition memory				Know				Remember			
	ON/Green		OFF/Blue		ON/Green		OFF/Blue		ON/Green		OFF/Blue	
	HR	FAR	HR	FAR	HR	FAR	HR	FAR	HR	FAR	HR	FAR
Parkinson's disease patients ($n = 23$)												
Mean	58.5	7.17	57.17	5.83	20.58	5.46	17.78	4.39	37.92	1.71	39.39	1.44
SD	28.96	7.86	22.12	5.95	10.9	5.01	6.49	3.95	18.06	2.85	15.63	2.0
Mild PD subgroup ($n = 12$)												
Mean	63.39	6.47	61.23	6.15	17	4.85	15.92	3.92	46.39	1.62	45.31	2.23
SD	22.02	6.92	22.15	5.99	7.21	4.56	6.24	3.64	14.81	2.36	15.91	2.35
Moderate PD subgroup ($n = 11$)												
Mean	50.1	7.7	51.9	5.4	26.2	5.9	20.2	5.0	23.9	1.8	31.7	0.4
SD	23.96	9.52	18.25	4.97	13.06	5.86	6.29	4.45	10.9	3.66	11.96	0.52
Healthy volunteers ($n = 21$)												
Mean	67.38	10.5	67	8.52	15.95	7.24	15.19	6.81	51.43	3.29	51.81	1.71
SD	19.26	11.9	22.79	8.19	6.76	7.3	8.36	6.77	12.5	4.56	14.43	1.42

Notes: HR, hit rate; FAR, false alarm rate; SD, 1standard deviation.

tion experience in terms of either feelings of familiarity without any recollection ('*know*' response) or a specific recollection of the item having been previously presented ('*remember*' response). The second stage was not time constrained. Participants were familiarized with the experimental set-up prior to completing both versions of the recognition memory task, and regular checks were made throughout the test phase to ensure that participants maintained a full understanding of the criteria for making a remember or know decision. The guidance for the *remember–know* decision is available on request from the lead author.

To examine the effect of dopaminergic medication on memory, patients were tested in a fully medicated and unmedicated state (termed ON and OFF, respectively). The healthy volunteers were also tested for 2 sessions, labelled "Blue" and "Green". This label

Table 3
Discrimination accuracy rates for recognition memory, familiarity and recollection rates in ON/Green and OFF/Blue conditions by group.

Group	HY	RM		Familiarity		Recollection		Group	RM		Familiarity		Recollection	
		ON	OFF	ON	OFF	ON	OFF		Green	Blue	Green	Blue	Green	Blue
PD 6	2	3.1864	3.085	2.131	2.295	0.79	0.79	HV 2	1.985	1.914	1.28	1.364	0.593	0.469
PD 7	2.5	3.118	3.577	2.209	2.66	0.778	0.84	HV 9	0.797	0.973	0.528	0.435	0.247	0.272
PD 9	2.5	2.1827	2.282	1.707	1.874	0.395	0.407	HV 10	2.118	3.085	0.775	2.203	0.667	0.901
PD 10	2.5	2.7874	2.787	2.263	1.843	0.494	0.654	HV 11	2.51	2.32	1.678	1.145	0.753	0.802
PD 11	1	3.6908	3.41	2.464	2.682	0.778	0.679	HV 1	3.246	3.288	2.345	1.993	0.642	0.691
PD 12	2	1.0152	1.678	0.775	1.4	0.235	0.333	HV 3	4.095	3.679	2.968	2.732	0.84	0.802
PD 16	2	0.9541	1.838	0.62	1.463	0.259	0.444	HV 4	3.954	4.095	3.214	3.285	0.802	0.765
PD 18	2	2.1106	2.156	1.622	1.599	0.469	0.457	HV 5	2.612	2.411	2.189	1.88	0.494	0.531
PD 19	2	2.7327	1.815	2.13	1.592	0.605	0.691	HV 6	2.983	2.096	2.756	1.276	0.691	0.642
PD 20	2	2.8167	2.209	1.959	1.842	0.469	0.247	HV 7	1.847	2.843	1.346	2.467	0.543	0.63
PD 22	2.5	2.4661	1.532	1.687	0.894	0.593	0.531	HV 12	0.693	1.059	0.646	0.679	0.222	0.37
PD 24	2	2.3773	1.952	1.251	1.196	0.753	0.568	HV 8	4.587	3.274	2.964	2.632	0.877	0.84
PD 1	3	2.0619	2.156	1.678	1.322	0.296	0.543	HV 13	0.74	1.303	0.635	1.008	0.185	0.272
PD 2	3	1.6216	1.64	0.957	1.24	0.309	0.321	HV 14	2.377	2.657	1.757	1.863	0.642	0.728
PD 3	3	1.4658	1.176	1.139	0.791	0.296	0.296	HV 15	2.09	2.277	1.129	1.183	0.691	0.605
PD 4	4	1.4723	1.715	1.62	1.099	0.235	0.346							
PD 5	3	2.2319	2.304	2.244	2.092	0.136	0.173	HV 16	3.213	3.274	2.113	2.292	0.741	0.79
PD 8	3	1.232	1.492	0.838	0.976	0.235	0.284	HV 17	1.939	1.538	1.412	1.162	0.358	0.395
PD 13	3	2.0543	1.684	1.462	1.333	0.21	0.259	HV 18	2.207	2.32	1.626	1.768	0.593	0.642
PD 14	3	2.1184	2.495	1.617	1.85	0.333	0.481	HV 19	2.697	2.343	1.923	1.557	0.63	0.63
PD 15	3	1.4179	1.575	1.308	1.026	0.185	0.272	HV 20	1.712	1.952	1.066	1.248	0.568	0.543
PD 17	4	1.9328	2.587	1.883	1.937	0.494	0.543							
PD 23	3	2.2067	2.272	1.57	1.521	0.568	0.617	HV 21	3.118	3.085	2.37	2.561	0.704	0.667
Mean	2.61	2.1486	2.141	1.614	1.588	0.431	0.469	Mean	2.453	2.466	1.749	1.749	0.594	0.618
SD	0.69	0.6219	0.711	0.515	0.523	0.209	0.186	SD	1.049	0.845	0.821	0.741	0.196	0.181
Mild PD subgroup ($n = 12$)														
Mean	2.08	2.360	2.453	1.735	1.778	0.551	0.553							
SD	0.42	0.691	0.817	0.589	0.548	0.198	0.183							
Moderate PD subgroup ($n = 11$)														
Mean	3.182	1.918	1.801	1.483	1.381	**0.3**[a,b,c]	**0.376**[a]							
SD	0.405	0.462	0.364	0.408	0.424	0.129	0.145							

Notes: Mild PD subgroup: PD 6, 7, 9–12, 16, 18–20, 22, 24; moderate PD subgroup: PD 1–5, 8, 13–15, 17, 23. SD, 1standard deviation; *d'*, signal detection index of discrimination accuracy; HR – FAR, hit rate minus false alarm rate providing a threshold measure of discrimination accuracy; HY, Hoehn and Yahr disease severity rating scale; RM, recognition memory; ON, medicated state; OFF, unmedicated state.

[a] Significantly impaired recollection rates compared to healthy volunteers.
[b] Significantly impaired recollection rates compared to mild Parkinson's at $p < 0.05$.
[c] Significantly impaired recollection rates compared to unmedicated moderate Parkinson's at $p = 0.005$.

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emphasized that there is no difference in "treatment" between the 2 sessions: the "Blue" was yoked to the OFF session of the PD patients, the "Green" to the ON session.

In the ON condition, patients were tested in the morning, 2 h after taking their first medication of the day. To produce the OFF state, patients were assessed at the same time of day having delayed their first morning medication. The time since last medication was 12–14 h. The order of RMT versions 1 and 2 were counterbalanced across the ON/Green and OFF/Blue sessions, and the order of the ON/Green and OFF/Blue sessions were counterbalanced across participants. The study was approved by South Staffordshire NHS Research Ethics Committee.

4. Results

Recognition memory, *know* and *remember* false alarm and hit rates for the Parkinson's and healthy volunteer groups are presented in Table 2. A trend for higher false alarms by patients in the medicated compared to the unmedicated condition is evident but not significant ($t(22) = -0.42$, $p = 0.68$).

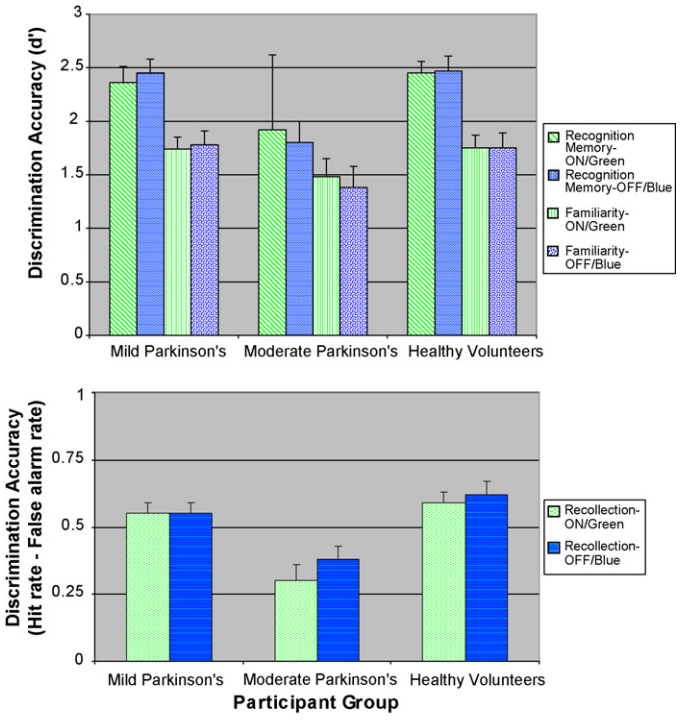
A correction has been made to the data to eliminate extreme scores in accordance with Snodgrass and Corwin's (1988) recommendation. It is assumed that recollection and familiarity are stochastically independent at retrieval, and therefore, Yonelinas and Jacoby's (1995) independence formula has been applied to the corrected *know* scores (familiarity = *know*/[1 − *remember*]). Estimates of overall recognition and familiarity discrimination accuracy were calculated using signal detection theory (*d'*), and a threshold measure of recollection is reported (hit rate minus false alarm rate).

Overall recognition, familiarity and recollection rates recorded during ON/Green and OFF/Blue sessions for the mild and moderate Parkinson's groups and healthy volunteers are presented in Table 3 and Fig. 1.

The data was first analyzed using a mixed 3 by 2 Multivariate Analysis of Covariance, with *Group* (healthy volunteers vs. mild Parkinson's vs. moderate Parkinson's) as the between-subjects factor, and *Condition* (ON/Green vs. OFF/Blue) the within subjects factor. Depression was the covariate and the dependent variables were the measures of recognition memory, familiarity and recollection.

There was a main effect of *Group* ($F(2,40) = 1.78$, $p = 0.035$), but not for *Condition* ($F(2,40) = 1.08$, $p = 0.39$), and the interaction failed to reach significance ($F(2,40) = 1.33$, $p = 0.25$, respectively). The between-subjects tests revealed a significant effect of *Group* on recollection (ON/Green: $F(2,40) = 7.47$, $p = 0.002$; OFF/Blue: $F(2, 40) = 4.81$, $p = 0.013$, respectively) but not on either recognition memory or familiarity (ON/Green recognition memory: $F(2,40) = 2.16$, $p = 0.13$; OFF/Blue recognition memory: $F(2,40) = 1.14$, $p = 0.33$; ON/Green familiarity: $F(2,40) = 0.06$, $p = 0.56$; OFF/Blue familiarity: $F(2,40) = 0.093$, $p = 0.4$, respectively).

Two one-way ANOVAs and Bonferroni post hoc tests investigated the locus of these effects further. In the ON/Green condition, there was no significant difference between the healthy volunteers and patients with mild Parkinson's, but both groups differed significantly from the moderate Parkinson's group ($ps < 0.05$). In the OFF/Blue condition there was no difference between the mild and moderate Parkinson's patients or between the mild Parkinson's and healthy volunteers, but the moderate Parkinson's patients differed significantly from the healthy volunteers ($p < 0.05$).



Notes: Error bars represent standard errors of the mean.

Fig. 1. Discrimination accuracy rates for recognition memory, familiarity (upper) and recollection (lower) in ON/Green and OFF/Blue conditions by group. *Notes*: Error bars represent standard errors of the mean.

The next set of analyses consisted of a series of within group paired *t*-tests examining the effect of medication on each of the 3 memory measures. In mild Parkinson's, medication had no effect on any of the memory measures (recognition memory: $t(11) = 0.56$, $p = 0.59$; familiarity: $t(11) = -0.32$, $p = 0.76$; recollection: $t(11) = -0.06$, $p = 0.96$). There was also no effect of medication on either recognition memory or familiarity in the moderate Parkinson's group ($t(10) = -1.35$, $p = 0.21$; $t(10) = 1.3$, $p = 0.22$, respectively). However, recollection rates were significantly poorer ON-medication compared to OFF ($t(10) = -3.58$, $p = 0.005$). Finally, the healthy volunteers showed no effect of condition (Green/Blue) on recognition memory, familiarity or recollection ($t(20) = -0.11$, $p = 0.92$; $t(20) = -0.01$, $p = 1.0$; $t(20) = -1.36$, $p = 0.19$, respectively).

Finally, *z*-scores were used to further explore the effect of disease severity on familiarity and recognition memory (see Table 4). Although a deficit in familiarity was not predicted, a subtle decline in this measure is consistent with the development of pathology in

Table 4
z-scores for recognition memory, familiarity and recollection rates in ON and OFF conditions by mild and moderate Parkinson's patients.

Group	ON-medication			OFF-medication		
	RM	Familiarity	Recollection	RM	Familiarity	Recollection
Mild PD subgroup ($n = 12$)						
z-score	−0.02	−0.03	−0.19	−0.18	−0.04	−0.48
Moderate PD subgroup ($n = 11$)						
z-score	−0.45	−0.26	−1.1	−0.44	−0.35	−0.98

Notes: *z*-scores are based on the healthy volunteer performance; RM, recognition memory.

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medial perirhinal cortex with relative sparing of lateral perirhinal areas.

~~Consistent~~ with expectations, *z*-scores for recognition memory and familiarity, show a subtle decline with disease severity. Furthermore, the relatively more pronounced decline in recollection compared to the other memory measures adds further evidence in support of the claim for a relatively greater involvement of recollection impairment in Parkinson's.

5. Discussion

Our study was designed to investigate the impact of disease severity and dopaminergic medication on the assessment of familiarity and the recollection of episodic details during recognition in patients with idiopathic, nondementing Parkinson's. Our predictions were derived from the convergence of three theories: the staging of α-synuclein pathology in Parkinson's (Braak et al., 2003); a dual process view of recognition memory (Aggleton & Brown, 1999, 2006; Yonelinas, 1994; see Yonelinas et al., 2002 for review); the l-dopa overdose hypothesis (Cools, 2006) and MR studies of hippocampal atrophy in patients at different stages of Parkinson's. Our central hypothesis was that the neural circuits on which recollection and familiarity depend are differentially affected by disease progression, and consequently, the effects of dopaminergic medication on familiarity and recollection will also differ.

Our first set of predictions, which applied to patients tested in an unmedicated state, were supported. The mild Parkinson's group displayed the expected sparing of both recollection and familiarity, whereas the dissociation between deficient recollection and (relatively spared) familiarity emerged in the moderate Parkinson's set. The second set of predictions, in contrast, were not supported. L-dopa neither remediated deficient recollection in moderate Parkinson's, nor did it impair the relatively preserved familiarity and recollection in mild Parkinson's. In fact, dopaminergic medication had the opposite effect to that predicted, with recollection rates showing a greater decline in medicated compared to unmedicated conditions.

It could be suggested that the failure of the l-dopa overdose hypothesis to accurately predict the pattern of recollection and familiarity in our cohort of patients may be due to the fact that we have recruited an unrepresentative sample, an argument used previously in relation to the recollection/familiarity profile reported by Barnes et al. (2003) and Davidson et al. (2006). However, we would argue against this suggestion on the grounds that the profile of our current empirical findings replicate two earlier dual process investigations of recognition memory in medicated patients (Edelstyn et al., 2007; Hay et al., 2002). So, for example, Hay et al. reported a significant decline in recollection from normal levels in mild Parkinson's to deficient levels in moderate Parkinson's; and Edelstyn et al. demonstrated a dissociation between significantly impaired recollection and spared familiarity in moderate Parkinson's patients compared to healthy controls.

There is also the possibility that the absence of an l-dopa overdose effect on relatively spared recollection in mild Parkinson's and familiarity in mild and moderate, predicted by the Yerkes-Dodson inverted U-shaped curve, was due to low levels of l-dopa in our patients. However, the fact that an l-dopa overdose effect on familiarity was also absent from the moderate Parkinson's group who were on a significant higher l-dopa dose argues against this proposal.

In addition to l-dopa, all but one of our patients were on adjuvant dopaminergic medication that included MAO-B inhibitors (selegiline or rasagiline), COMT inhibitors (tolcapone or entacapone) and second generation nonergoline dopamine agonists (ropinirole hydrochloride, pramipexole hydrochloride or rotigotine). It is possible therefore, that the further decline of recollection in our medicated moderate Parkinson's group, may stem ~~from withdrawal~~ from one of these alternative dopamine enhancers in addition to l-dopa. Studies examining the action of these classes of medication on episodic memory are limited, but the consensus from animal studies suggests that neither MAO-B inhibitors nor COMT inhibitors are likely to be contributory factors. Selegiline, for example, appears to protect rather than impair spatial memory in rats (e.g., Martins de Lima et al., 2005). Similar findings have also been noted for tolcapone (e.g., Liljequist, Haapalinna, Ahlander, Li, & Mannisto, 1997).

A small number of studies have examined the effects of second generation nonergoline dopamine agonists on cognitive function. The focus has primarily been on pramipexole, where the dopamine agonist has been shown to both improve performance on working memory and task switching tasks but impair certain forms of probabilistic reversal learning (Cools, Altamirano, & D'Esposito, 2006; Cools et al., 2001; Costa, Peppe, Dell'Agnello, Caltagirone, & Carlesimo, 2009). Pramipexole has also been linked with the development of pathological gambling in a subset of Parkinson's patients (Driver-Dunckley et al., 2003; Dodd et al., 2005). Although neither our patients, nor their carers, reported any overt risk-taking behaviour since commencing pharmacotherapy, it is possible that their behaviour on the recognition memory tests may have been affected, for example, by the adoption of a more liberal mode of responding. Although false alarm rates were not significantly elevated in the ON condition, there was a trend for higher rates in the ON condition. A larger sample, subdivided by disease severity and medication class as well as type, will be able to clarify this matter further.

From a theoretical perspective, the finding that dopaminergic medication leads to a selective decline in recollection and with relatively greater sparing of familiarity is consistent with the view that these component recognition memory processes are supported by separate neural networks. The Aggleton and Brown (1999, 2006) model assigns the perirhinal cortex and its projection site, the mediodorsal thalamus, a specific role in the mediation of familiarity during recognition. This network is distinct from an extended hippocampal system involving the fornix, mammillary bodies, mammillothalamic tract, and anterior thalamus that supports free recall and the recollection of episodic details during recognition. According to this model, damage to the hippocampus in the presence of relative sparing of the perirhinal cortex should be marked by a selective impairment in the recollection and preservation of familiarity. This pattern of impairment is present in our moderate Parkinson's group when tested both ON- and OFF-medication.

The robustness of our reported dissociation between spared familiarity and deficient recollection in the moderate Parkinson's group has a striking similarity to the reports of patients with selective lesions of the hippocampus (e.g., Aggleton et al., 2005; Bastin et al., 2004; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Mayes et al., 2004; Vargha-Khadem et al., 1997; Yonelinas et al., 2002) and fornix (Tsivilis et al., 2008; Vann et al., 2009) who are able to perform normally on familiarity/recognition in the face of impaired recollection/recall tasks; and functional brain imaging reports of healthy volunteers showing the hippocampus is critical to the recollection of episodic detail during recognition (e.g., Montaldi, Spencer, Roberts, & Mayes, 2006). Furthermore, the presence of other groups of lesion patients with damage to the perirhinal cortex (Bowles et al., 2007; ~~Haskins, Yonelinas, Quamme, & Ranganath, 2008;~~ see reviews by Eichenbaum, Yonelinas, & Ranganath, 2007; Mayes, Montaldi, & Migo, 2007) that spares the hippocampus indicates that familiarity/recognition and recollection/recall can doubly dissociate in patient groups with different medial temporal lobe and diencephalic pathology.

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In sum, the results of the current study demonstrate that nondementing moderate Parkinson's can selectively impair the recollection of episodic details during recognition. Together with past findings showing that hippocampal lesions can result in a dissociation between (deficient) recollection and (preserved) familiarity, our study provides further support for a dual- rather than single dimension account in which recollection and familiarity are separate processes that are combined into a single dimension (see Dunn, 2004; Wixted, 2007; Wixted & Stretch, 2004; for arguments supporting a single dimension account). Our results also raise the possibility that this recollection deficit may be exacerbated by routine dopaminergic medication used to control motor symptoms in Parkinson's. This finding argues against the l-dopa overdose hypothesis and raises the possibility that overactivation or abnormal stimulation of postsynaptic dopamine receptors by second generation nonergoline dopamine agonists may play a contributory role.

Q5 Uncited references

Kartsounis, Rudge, and Stevens (1995), Lewis et al. (2005), and Davies, Matthews, Stammers, and Westerman (2000).

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